REMARKS/ARGUMENTS

Status of the Claims

Claims 13-20, 25, 26, and 29-40 were originally pending in this application. Claims 15, 19, 20, and 30-40 were withdrawn in response to a restriction requirement and have now been canceled. Claim 16 has now been canceled. Claims 13, 14, 17-18, 25-26, and 29 are now pending. Claims 13, 14 and 26 have been amended. No new matter has been entered by way of amendment. An objection was set forth in the Office Action with respect to the specification. The specification has been amended. Applicant asks that all claims be examined and allowed.

Claim Objections

The Examiner has objected to Claim 14 as containing non-elected inventions. Claim 14 has been amended to remove non-elected inventions. Applicant requests that the objection be withdrawn. The Examiner also objected to Claim 16 as being a duplicate of Claim 14. Claim 16 has now been canceled. The Applicant requests withdrawal of the objection.

Objection to the Specification

The Examiner has objected to certain informalities in the specification. The Applicant has amended the specification to correct the informalities. Applicant respectfully requests that the objection to the specification be withdrawn.

The Rejections of Claims 26 and 29 Under 35 U.S.C. §112 Should be Withdrawn

Claims 26 and 29 were rejected under 35 U.S.C. 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention. The Examiner objects to Claim 26 as reciting the limitation "ductal fluid samples" without antecedent basis in Claim 13. Claim 26 has been amended to recite a "ductal fluid sample". The Examiner has also objected to Claim 29 as reciting the limitation "the single lumen" without antecedent basis in Claim 13. Claim 13 has been amended to recite a "single lumen." Withdrawal of the objections under 35 U.S.C. 112, second paragraph is respectfully requested.

The Rejections Under 35 U.S.C. §103(a) Should be Withdrawn

Claims 13, 14, 16-18, 25, 26 and 29 were rejected under 35 U.S.C. § 103(a) as being unpatentable over JAMA (1973, 224(6):823) in view of Love et al. (Lancet 1996, 348:997-999), Hou et al. (Radiology, 1995, 195(2): 568-569) and U.S. Patent No. 6,287,790. The rejection of claims 13, 14, 17, 18, 25, 26 and 29 is traversed. Claim 17 has been canceled rendering the Examiner's objection moot.

JAMA (1973, 224(6):823) (hereinafter referred to as "Sartorius") makes reference to a method being developed by Dr. Sartorius which consists of inserting hair-like catheters (which are 0.0065 mm in diameter) into breast ducts with the help of an operating microscope. Once the microcatheter has been inserted into a breast duct, the ducts are flushed out with saline. There is no mention in the article of how the fluid from the flushing procedure is captured. The Examiner argues that the Sartorius reference teaches a method comprising inserting hair-like catheters into

breast ducts, flushing the ducts with saline for cell studies and examining the fluid from each duct separately. The Examiner also states that the Sartorius reference teaches that the ductal fluid sample contains usable cells and that the fluids are also tested for reverse transcriptase, a possible cancer marker. The Examiner further admits that the Sartorius reference does not teach the collection of a sample from a plurality of ducts, the detection of NuMA using an antibody, as well as retrieving a sample through a lumen which has an internal diameter large enough to retrieve clusters of greater than 10 cells. The Applicant also would point out that Sartorius does not teach or suggest the use of a single lumen catheter (found in newly amended claim 13), as well as examining the ductal fluid sample to determine the presence of a marker (also found in newly amended claim 13).

Thus, Sartorius does not teach or suggest all of the limitations of the present claims including the use of a single lumen catheter as well as determining the presence of a marker in a fluid sample. The Examiner argues that these deficiencies are made up for in the teachings of Love et al., Hou et al., and USP 6,287,790. The Applicant disagrees.

Love, et al. (Lancet 1996, 348:997-999) teaches a method of using endoscopy to study stages of cancerous breast disease. The Examiner argues that Love et al. teaches a method of collecting ductal fluid from a breast comprising inserting a cannula into one or more breast ducts, infusing saline into the breast ducts, collecting the washings from the ducts and analyzing the washings cytologically. Love et al. does not teach or suggest the use of a single lumen catheter to introduce and remove wash fluid from a breast duct. In fact, as pointed out by the Examiner (Office Action page 8), Love et al. teaches away from the use of a catheter to remove ductal washings because as stated in Love et al. "...the duct is so small...that it is difficult to aspirate back through the cannula to obtain material. When washing, we removed the catheter and

collect the fluid externally in a capillary tube." (page 998, 2nd paragraph). Thus, Love et al. does not teach or suggest the use of a single lumen catheter to introduce and remove wash fluid from a breast duct, as well as examining the ductal fluid sample to determine the presence of a marker.

Hou et al. (Radiology, 1995, 195(2): 568-569) teaches a method of duct cannulation for galactography before excision of a patient's breast. Hou et al. does not teach or suggest the use of a single lumen catheter to introduce and remove wash fluid from a breast duct for the purpose of analyzing the contents of the wash solution.

USP 6,287,790 issued to Lelievre, et al. (hereinafter referred to as Lelievre et al.) teaches the localization of nuclear apparatus proteins (NuMA) to identify tumor cells and different stages in the tumor progression and differentiation processes. Lelievre et al. does not teach or suggest that the presence of NuMA in a ductal fluid sample can be used as a marker for determining a cancerous or precancerous condition in the breast of a patient. Lelievre et al. mere examines the localization of NuMA within cell lines. There is simply no mention is the

Applicants respectfully traverse the foregoing rejection on the grounds that the Examiner has failed to establish a *prima facie* case of obviousness, since Sartorius, Love et al., Hou et al., or Lelievre et al. alone or in combination, fail to teach or suggest the claimed invention and further fail to provide the necessary motivation or expectation of success for the ordinarily skilled artisan to arrive at the claimed invention.

To establish a prima facie case of obviousness, it is necessary for the Examiner to present evidence, preferably in the form of some teaching, suggestion, incentive or inference in the applied references, or in the form of generally available knowledge, that one having ordinary skill in the art would have been motivated to make the claimed invention and would have had a reasonable expectation of success in making the claimed invention. Under section 103, "[b]oth

the suggestion and the expectation of success must be founded in the prior art, not in applicant's disclosure" (*Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.* 927 F.2d 1200, 1207, 18 USPQ2d 1016 (Fed. Cir. 1991), quoting *In re Dow Chemical Co.,* 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed Cir. 1988)). Moreover, when a combination of references are used to establish a *prima facie* case of obviousness, the Examiner must present evidence that one having ordinary skill in the art would have been motivated to combine the teachings in the applied references in the proposed manner to arrive at the claimed invention. See, *e.g.*, *Carella v. Starlight Archery*, 804 F.2d 135, 231 USPQ 644 (Fed. Cir. 1986); and *Ashland Oil, Inc. v. Delta Resins and Refractories, Inc.*, 776 F.2d 281, 227 USPQ 657 (Fed. Cir. 1985).

Applying this standard to the references cited by the Examiner, it is clear that the Examiner has failed to meet the burden of providing evidence of a motivating force sufficient to impel a person of ordinary skill in the art to combine the teachings of Sartorius, Love et al., Hou et al., or Lelievre et al. to arrive at the claimed invention. As mentioned previously, Sartorius does not teach or suggest all of the limitations of the present claims including the use of a single lumen catheter as well as determining the presence of a marker in a fluid sample.

The Examiner argues that these deficiencies are made up for in the teachings of Sartorius, Love et al., Hou et al., and Lelievre et al. In particular, the Examiner states that a person of ordinary skill in the art would have been motivated to combine the teachings Sartorius, Love et al., Hou et al., and Lelievre et al. because "...[Sartorius] and Love teach method of diagnosing breast cancer by isolating a ductal fluid from one or more breast ducts by ductal lavage and further detecting a cancer marker in the isolated ductal fluid, Hou teaches retrieving the solution from the duct through the catheter and [Lelievre et al.] teaches that NuMA is a breast cancer

marker that can be used to identify breast tumor cells and different stages in the breast tumor progression and differentiation processes." The Applicant disagrees.

First, neither Sartorius nor Love et al. teach or suggest a method of introducing and retrieving a sample from a breast duct via a single lumen catheter. In fact, Love et al. specifically teaches that the use of a single lumen catheter does not work when trying to aspirate a sample back through a catheter disposed within a duct of a breast and thus a different methodology had to be used to obtain a sample. The Examiner suggests that such a deficiency may be made up by Hou et al. The Applicant disagrees. Hou et al. does not teach or suggest the introduction and retrieval of a ductal lavage solution from a duct through a catheter. Hou et al. teaches a method for introducing a dye into a breast duct solely for the purpose of galactography. Once the dye has been introduced and the galactography procedure is finished, the dye is removed and discarded. There is nothing in Hou et al. that teaches or suggests that the dye removed from the duct after the procedure is over contains any cellular material or markers that would be useful in detecting cancer or precancer.

The Examiner states that one skilled in the art would have a reasonable expectation of success to combine the teachings Sartorius, Love et al., Hou et al., and Lelievre et al. The Applicant disagrees. Love et al. specifically teaches that the use of a single lumen catheter does not work when trying to aspirate a sample back through a catheter disposed within a duct of a breast. Hou et al. teaches the removal of dye from a breast duct during a completely different procedure. Why would one of skill in the art believe that the teaching of Hou et al., using a completely different and unrelated methodology, would provide a greater expectation of success than the teaching of Love et al. which is directly on point and unequivocally states that the aspiration of solution from a duct through a catheter does not work? The Applicant submits that

the Examiner has not presented clear and convincing evidence that one having ordinary skill in the art would have been motivated to combine the teachings in the applied references in the proposed manner to arrive at the claimed invention. Since there is no teaching or suggestion of the introduction and retrieval of a ductal lavage solution from a duct through a single lumen catheter in Sartorius, Love et al., and Hou et al., the Applicant respectfully submits that the Examiner has, at most, set forth an "obvious to try" rationale in support of this obviousness rejection. However, an "obvious to try" rationale is not the appropriate standard for obviousness under 35 U.S.C. §103 (M.P.E.P. §2145).

Second, neither Sartorius nor Love et al. teach or suggest detecting the presence of a cancer marker in the isolated ductal fluid. Sartorius mentions that the testing for elevated levels of the enzyme reverse transcriptase may be implicated as a possible cancer marker. Thus, the presence of reverse transcriptase in a fluid sample is used in Sartorius to classify women who are at "high risk" of getting breast cancer. As mentioned in Sartorius, women who use oral contraceptives have high titers of reverse transcriptase but they do not necessarily have cancer. Thus, the "marker" used in Sartorius is not used to determine the presence of cancer in a patient. The same holds true for Love et al. Love et al. uses positive membrane neu immunoreactivity, positive nuclear p53 immunoreactivity or aneuploidy to confirm a previous diagnosis of DCIS. The "markers" as taught in Love et al. were not used for identifying a patient having breast cancer or breast precancer. Thus, the Examiner's argument that Sartorius and Love teach method of diagnosing breast cancer by isolating a ductal fluid from one or more breast ducts by ductal lavage and further detecting a cancer marker in the isolated ductal fluid is not supported by the evidence.

Lastly, Lelievre et al. does not teach or suggest that NuMA is a breast cancer marker that can be used to identifying a patient having breast cancer or breast precancer. As mentioned previously, Lelievre et al. teaches the use of NuMA as a marker for examining the different stages in the breast tumor progression. There is simply no teaching or suggestion in Lelievre et al. that NuMA could be used as a diagnostic marker for the presence of cancer. Thus, the Examiner's argument that NuMA is a breast cancer marker that can be used to identify breast tumor cells is not supported by the evidence.

In view of the foregoing, Applicants respectfully submit that Sartorius, Love et al., Hou et al., and Lelievre et al., alone or in combination, fail to teach or suggest a method for identifying a patient having breast cancer or breast precancer comprising placing a ductal access tool comprising a single lumen in a breast duct of a patient; infusing a fluid into the duct through the single lumen; retrieving a ductal fluid sample from the accessed duct through the single lumen; and examining the ductal fluid sample to determine the presence of a marker comprising an expression product of a gene encoding a nuclear matrix protein, as recited in the claims. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 13, 14, 16-18, 25, 26 and 29 under 35 U.S.C. § 103(a).

The Rejections Under 35 U.S.C. §103(a) Should be Withdrawn

Claims 13, 14, 16-18, 25, 26 and 29 were rejected under 35 U.S.C. § 103(a) as being unpatentable over USP 6,221,622 in view of Love et al. (Lancet 1996, 348:997-999), Hou et al. (Radiology, 1995, 195(2): 568-569) and U.S. Patent No. 6,287,790 (Lelievre et al.) The rejection of claims 13, 14, 17, 18, 25, 26 and 29 is traversed. Claim 17 has been canceled rendering the Examiner's objection moot.

USP 6,221,622 to Love (hereinafter '622 patent) teaches a method of assessing the likelihood of a cancer in the cellular lining of a breast duct, the method comprising: locating at least one of the ductal orifices on a nipple of the breast; introducing a catheter having at least two lumens through one of the ductal orifices and into the ductal passage; introducing a washing fluid through a lumen into the ductal passage; collecting the washing fluid from the ductal passage through a lumen of the catheter while the catheter is within the ductal passage, wherein the material in the collected fluid include epithelial cells; and examining the morphology of the epithelial cells in the collected fluid to determine if they are atypical in order to assess the likelihood of a cancer present in the cellular lining of the duct. The '622 patent teaches the use of a dual lumen catheter which was developed to overcome the technical problems encountered when using a single lumen catheter (as described in Love, et al. (Lancet 1996, 348:997-999)). There is no mention of the use of a single lumen catheter to introduce and retrieve fluid samples from a breast duct. As mentioned in great detail above, this deficiency cannot be made up for in the teachings of Love et al., Hou et al., and Lelievre et al.

In view of the foregoing, Applicants respectfully submit that the '622 patent, Love et al., Hou et al., and Lelievre et al., alone or in combination, fail to teach or suggest a method for identifying a patient having breast cancer or breast precancer comprising placing a ductal access tool comprising a single lumen in a breast duct of a patient; infusing a fluid into the duct through the single lumen; retrieving a ductal fluid sample from the accessed duct through the single lumen; and examining the ductal fluid sample to determine the presence of a marker comprising an expression product of a gene encoding a nuclear matrix protein, as recited in the claims. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 13, 14, 16, 18, 25, 26 and 29 under 35 U.S.C. § 103(a).

The Rejections Under 35 U.S.C. §103(a) Should be Withdrawn

Claims 13, 14, 16-18, 25, 26 and 29 were rejected under 35 U.S.C. § 103(a) as being unpatentable over USP 6,494,859 in view of Love et al. (Lancet 1996, 348:997-999), Hou et al. (Radiology, 1995, 195(2): 568-569) and U.S. Patent No. 6,287,790 (Lelievre et al.) The rejection of claims 13, 14, 17, 18, 25, 26 and 29 is traversed. Claim 17 has been canceled rendering the Examiner's objection moot.

USP 6,494,859 to Love (hereinafter '859 patent) teaches a method of assessing the likelihood of a cancer in the cellular lining of a breast duct, the method comprising: locating at least one of the ductal orifices on a nipple of the breast; introducing a catheter having at least two lumens through one of the ductal orifices and into the ductal passage; introducing a washing fluid through a lumen into the ductal passage; collecting the washing fluid from the ductal passage through a lumen of the catheter while the catheter is within the ductal passage, wherein the material in the collected fluid include epithelial cells; and examining the morphology of the epithelial cells in the collected fluid to determine if they are atypical in order to assess the likelihood of a cancer present in the cellular lining of the duct. The '859 patent (a continuation of the '622 above) teaches the use of a dual lumen catheter which was developed to overcome the technical problems encountered when using a single lumen catheter (as described in Love, et al. (Lancet 1996, 348:997-999)). There is no mention of the use of a single lumen catheter to introduce and retrieve fluid samples from a breast duct. As mentioned in great detail above, this deficiency cannot be made up for in the teachings of Love et al., Hou et al., and Lelievre et al.

In view of the foregoing, Applicants respectfully submit that the '622 patent, Love et al., Hou et al., and Lelievre et al., alone or in combination, fail to teach or suggest a method for identifying a patient having breast cancer or breast precancer comprising placing a ductal access tool comprising a single lumen in a breast duct of a patient; infusing a fluid into the duct through the single lumen; retrieving a ductal fluid sample from the accessed duct through the single lumen; and examining the ductal fluid sample to determine the presence of a marker comprising an expression product of a gene encoding a nuclear matrix protein, as recited in the claims. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 13, 14, 16, 18, 25, 26 and 29 under 35 U.S.C. § 103(a).

CONCLUSION

It is believed that no extension is required for this submission. If any additional fees are required or if an overpayment is made, the Commissioner is authorized to debit or credit our Deposit Account No. 502855, accordingly. If any questions or issues remain, the resolution of which the Examiner feels would be advanced by a conference with Applicant, the Examiner is invited to contact Applicant's attorney at the number noted below.

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Respectfully submitted,

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